REMARKS

Reconsideration is requested.

Claims 41 and 43-93 are pending. Claims 52-93 have been withdrawn from consideration.

Claim 41 has been revised, without prejudice based on, for example, page 53, line 6 to page 55, line 17 and page 57, lines 12-17 of the specification. No new matter has been added.

The Section 112, first paragraph "enablement", rejection of claims 41 and 43-51 is obviated by the above amendments, as suggested by the Examiner in ¶6 on page 3 of the Office Action dated February 18, 2010. Entry of the present Amendment will at least reduce this issue for appeal. Entry of the Amendment and withdrawal of the Section 112, first paragraph "enablement", rejection are requested.

The Section 112, first paragraph "written description", rejection of claims 41 and 43-51 is obviated by the above amendments. The phrase which the applicants understand to be the basis of the rejection has been deleted, without prejudice. Entry of the present Amendment and withdrawal of the rejection are requested.

The Section 102 rejection of claims 41, 43-47 and 49-51 over Lin (EP 0778023) is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing remarks.

The Examiner is understood to believe that the claims do not define a patient group which is novel over the patient group disclosed in Lin et al. In particular the

Examiner is understood to suggest that the applicants have allegedly failed to provide guidance as to who may be in need of the claimed treatment and that the ordinarily skilled person would allegedly "reasonably construe 'prophylactic treatment' as reducing the severity of HD" (i.e., Huntington's disease), which is taught in Lin et al. See page 5 of the Office Action dated February 18, 2010.

Claim 41 describes a patient group as those who are "at risk of developing a protein conformational disorder". The applicants submit, with due respect, that unlike other types of disease, persons of ordinary skill in the art can readily identify patients who are "at risk of" developing a protein conformational disorder using straightforward techniques.

Individuals at high risk of developing Huntington's disease, forms of Parkinson's disease and other protein conformational disorders (including various spinocerebellar ataxias) have specific mutations in certain intracellular proteins which render these proteins highly prone to aggregation. The mutations associated with each disease are well-known and characterized in the art. For example, in Huntington's disease, excessive numbers of trinucleotide repeats in the polyQ region of the huntingtin gene lead to the production of a variant huntingtin protein with an abnormal number of polyQ repeats which is prone to aggregation.

The presence of a variant gene which contains excessive numbers of trinucleotide repeats is detected easily by routine genetic methods. Because the variant

gene which causes Huntington's disease is dominant, any individual who is found to possess the mutant huntingtin gene is at risk of developing Huntington's disease.

The identification of patients who are at risk of suffering from protein conformational disorder, such as Huntington's disease, is therefore straightforward and can be performed by one of ordinary skill in the art by routine genetic testing to determine the presence or absence of well-documented aggregation-causing mutations.

Lin et al describes the treatment of individuals who are suffering from neurodegenerative diseases, such as Huntington's disease, by inhibiting neuronal cell death. Lin et al lacks any disclosure of the treatment of individuals who are not suffering from a neurodegenerative disease but are "at risk of" suffering from a neurodegenerative disease. For example, page 2, lines 28-30, of Lin et al states:

> "…drugs that can prevent neuronal cell death following the rise in intracellular calcium are appropriate for the delayed treatment of stroke and head injuries, as well as for chronic treatment of neurodegenerative diseases." [emphasis added].

The applicants submit that the chronic treatment of neurodegenerative disease is distinct from the treatment of "at risk" individuals to delay the onset of neurodegenerative disease. The teaching of Lin et al directs one of ordinary skill towards this chronic treatment.

Furthermore, the experiments described in Lin et al do not provide any teaching of the treatment of "at risk" individuals to delay the onset of neurodegenerative disease.

The Examiner alleged that the protocol disclosed in Lin et al is not an *in vitro* treatment protocol because the cells are co-incubated with both rapamycin and

glutamate *"which induces protein aggregation"* (see page 5 of the Office Action dated February 18, 2010), so the cells have not already developed protein aggregates when they are treated with rapamycin.

However, while the Examiner is correct in stating that the cells in the Lin et al protocols are co-incubated with both rapamycin and glutamate, the Examiner is submitted to be incorrect in asserting that glutamate induces protein aggregation.

The applicants believe that the protocol described in Lin et al relates to *in vitro* glutamate toxicity. Glutamate has no effect on protein aggregation. Lin et al teaches on page 2 lines 21 to 24 that excess extracellular glutatamate causes overstimulation of NMDA receptors on neurons, leading to an influx of calcium into the cells. The resultant increase in intracellular calcium levels initiates cell death. Glutamate toxicity is therefore unrelated to protein aggregation and glutamate does not induce protein aggregation in cells. In the absence of any agent which induces protein aggregation, the treated cells do not contain protein aggregates at any stage of the protocols of Lin et al.

The Lin et al protocols provide a model of glutamate toxicity and not protein aggregation. Furthermore, the Lin et al protocols model acute glutamate toxicity (hippocampal neurons incubated with 30 to 150 μM glutamate overnight). Although chronic glutamate toxicity has been implicated in the cell death associated with neurodegenerative disease, acute glutamate toxicity models are, in fact, clinically meaningless and have no relevance to neurodegenerative diseases. The ordinarily

skilled artisan would not be able to draw conclusions about the clinical significance of rapamycin from these experiments.

In fact, intracellular protein aggregates or oligomeric precursors of the aggregates are the primary toxic entity in protein conformational disorders such as Huntington's disease (See Legleiter J et al J. Biol. Chem (2010) epub PMID: 20220138 "Mutant Huntingtin Fragments Form Oligomers in a Polyglutamine Length-Dependent Manner *In Vitro* and *In Vivo*" - copy attached). These oligomers/aggregates exert their toxic effects through a range of distinct and parallel pathways (see page 57 line 32 to page 58 line 9 of the instant specification), including glutamate toxicity occurs after intracellular protein oligomers/aggregates have formed and already rendered the affected neurons dysfunctional.

Even if neuronal cell death was entirely mediated by glutamate, any inhibition of neuronal cell death would simply extend the life of dysfunctional neurons. Since the neurons would still be dysfunctional, this would be unlikely to have any clinical impact on the disorder. By contrast, the present invention relates to reductions in the levels of intracellular proteins which are prone to aggregate and form the primary toxic entity in protein conformational disorders. A reduction in the formation of the primary toxic entity, as described in the instant specification, affects all downstream pathways of the disorder and is effective in delaying the onset of the disorder. This is demonstrated experimentally using *in vivo* models in the instant specification (see page 53 line 20 to page 55 line 2).

Even supposing the models of Lin et al were relevant to protein conformational disorders, neuronal cell death is a downstream pathological event which occurs after the onset of the disorder. Reducing neuronal cell death would have no effect on the formation of protein oligomers which are the primary toxic entity in the disorder or the progressive neuronal dysfunction which is caused by these structures.

In teaching an effect on glutamate-mediated cell death, Lin et al is teaching a treatment which targets downstream pathological events which only occur after the protein conformational disorder is established. The treatment would not affect the onset of the disorder, since it does not target pathological events which occur before or at the onset of the protein conformational disorder.

One of ordinary skill in the art would therefore understand Lin et al to teach that rapamycin has a therapeutic effect on individuals with neural conditions associated with glutamate induced toxicity by inhibiting the mechanism by which the condition causes neuronal cells to die.

Insofar as one of skill in the art may recognize the acute glutamate toxicity model of Lin et al as relevant to protein conformational disorders, this relevance would be confined to treatment of patients suffering from an established protein conformational disorder, in which neuronal cell death occurs.

One of ordinary skill in the art would find neither suggestion nor teaching in Lin et al to suggest that rapamycin macrolides or other autophagy stimulators might be

effective in individuals at risk of a protein conformational disorder to delay the onset of the disorder and reduce its subsequent severity.

The claims are submitted to be patentable over the cited art and withdrawal of the Section 102 rejection is requested.

The Section 103 rejection of claim 48 over Lin is traversed. Reconsideration and withdrawal of the rejection are requested in view of the above as claim 48 is dependent from claim 41 which is patentable over the cited art for the reasons noted above. Lin et al contains neither suggestion nor teaching that rapamycin macrolides or other autophagy stimulators might be effective in individuals at risk of a protein conformational disorder to delay the onset of the disorder and reduce its subsequent severity. Withdrawal of the Section 103 rejection is requested.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested. The Examiner is requested to contact the undersigned, preferably by telephone, in the event anything further is required.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: /B. J. Sadoff/
B. J. Sadoff
Reg. No. 36,663

BJS:pp
901 North Glebe Road, 11th Floor
Arlington, VA 22203-1808
Telephone: (703) 816-4000
Facsimile: (703) 816-4100